Right-sided heart failure in acute respiratory distress syndrome

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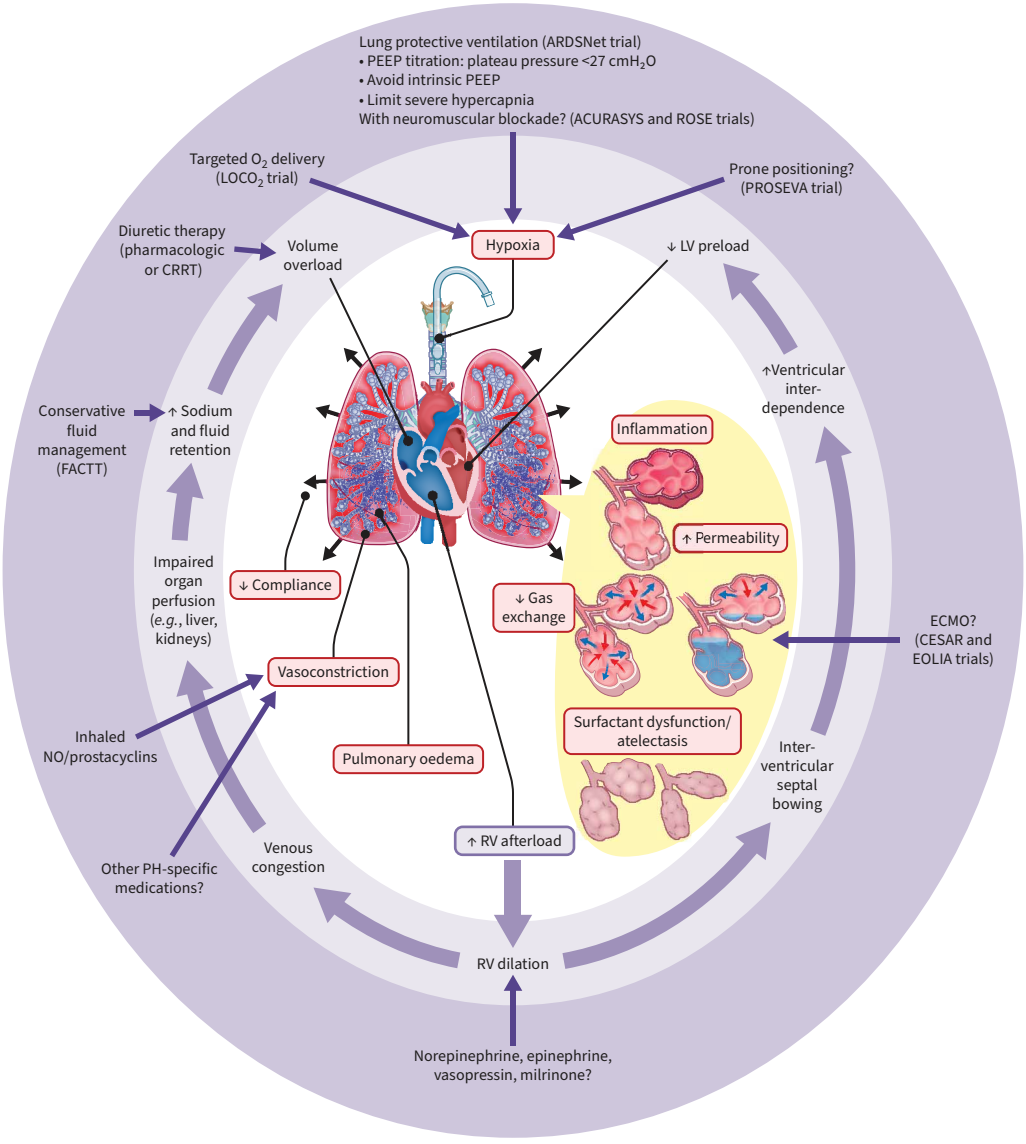

GRAPHICAL ABSTRACT Pathophysiology and management of right-sided heart dysfunction (RHD) in acute respiratory distress syndrome (ARDS). Pulmonary changes in ARDS contribute to increased right ventricular (RV) afterload and RV dysfunction (centre), which in turn lead to systemic venous congestion and reduced left ventricular (LV) preload (inner ring). Current/potential approaches for the treatment of patients with ARDS and RHD are summarised in the outer ring. CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; NO: nitric oxide; PEEP: positive end-expiratory pressure; PH: pulmonary hypertension.

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Right-sided heart dysfunction (RHD) has emerged as a critical yet often underappreciated aspect of acute respiratory distress syndrome (ARDS). This review describes the role of RHD in ARDS, covering its pathophysiology, diagnosis and potential treatments. https://bit.ly/45NrBgs

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Abstract

Right-sided heart dysfunction (RHD) has emerged as a critical yet often underappreciated aspect of acute respiratory distress syndrome (ARDS). This review describes the role of RHD in ARDS, providing an updated overview of its pathophysiology, diagnosis and potential treatments. Several mechanisms contribute to increased right ventricular (RV) afterload in ARDS, including hypoxic vasoconstriction, hypercapnia, acidosis, *in situ* thrombosis and an imbalance between pulmonary vasoconstrictors and vasodilators. Mechanical ventilation, a cornerstone in ARDS management, can worsen haemodynamic instability due to impaired lung compliance. Systemic implications of RHD include renal dysfunction due to impaired organ perfusion and venous congestion. Volume overload further exacerbates RV strain, setting off a vicious cycle of deteriorating RV function, interventricular septal bowing, reduced left ventricular preload and ultimately circulatory failure. The diagnosis and management of RHD in ARDS require an integrated approach that combines invasive haemodynamic monitoring, imaging techniques and noninvasive assessments. Specific treatment options targeting RHD in ARDS remain limited. Titration of positive end-expiratory pressure plays a critical role in mitigating RHD. Prone positioning has shown inconsistent effects on RV function which require further investigation. Inhaled pulmonary vasodilators, such as nitric oxide and prostacyclins, are commonly used to modulate pulmonary vascular tone in ARDS. Small studies suggest that levosimendan and commonly used vasoactive drugs such as norepinephrine, epinephrine, vasopressin and milrinone may improve RV function in ARDS. However, no pharmacologic treatment is specifically approved for ARDS-associated RHD. Large-scale clinical trials are necessary to identify the most effective treatment strategies for specific patient populations.

Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterised by acute-onset hypoxaemia and noncardiogenic pulmonary oedema [1, 2]. The Berlin definition classifies ARDS based on the severity of oxygenation impairment, providing a standardised framework for diagnosis [1]. Despite significant advances in ARDS management, including lung-protective ventilation, prone positioning, fluid restriction, mechanical support and, in select cases, neuromuscular blockade, mortality rates remain alarmingly high in both prospective clinical trials and retrospective registry analyses [3–11].

In this context, right ventricular (RV) dysfunction has emerged as a critical yet often underappreciated aspect of ARDS [12]. Notably, studies report that approximately 20–50% of patients with ARDS exhibit signs of RHD [13–15]. The right side of the heart, once considered secondary in circulatory physiology, plays an important role in adapting to the haemodynamic challenges imposed by ARDS. The hallmark pathophysiological mechanisms of ARDS, including hypoxic pulmonary vasoconstriction, pulmonary microvascular thrombosis and mechanical ventilation-induced increases in intrathoracic pressure, lead to a rise in mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), placing significant strain on the right ventricle [12, 16–19]. This can result in RV dilation, impaired systolic and

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diastolic function, and ultimately right-sided heart failure, which has been associated with poor clinical outcomes in patients with ARDS [13–15, 20–22].

Management of ARDS, including mechanical ventilation and prone positioning, significantly affects right heart function. Initially, the RV compensates for increased afterload through homeometric adaptation, primarily by enhancing contractility to maintain stroke volume [23]. However, in the setting of an acute or excessive rise in afterload, this mechanism becomes insufficient. To preserve stroke volume, the RV then shifts to heterometric adaptation, relying on chamber dilation to sustain forward flow [23]. Treatment largely focuses on optimising RV preload, afterload and contractility, while avoiding both volume overload and underfilling. However, specific therapies for RHD in ARDS remain limited. Strategies such as careful positive end-expiratory pressure (PEEP) titration, RV-protective ventilation and prone positioning may support RV function, though data are inconsistent. Inhaled pulmonary vasodilators (*e.g.* inhaled nitric oxide (iNO) and prostacyclins) and vasoactive agents (*e.g.* norepinephrine and milrinone) may improve RV–pulmonary artery (RV-PA) coupling, yet their benefits are often transient. Venovenous extracorporeal membrane oxygenation (VV-ECMO) can support gas exchange in severe ARDS, but its effects on RV function are variable. Overall, targeted therapies for RHD in ARDS are lacking and further research is urgently needed.

Historically, the relevance of RV function in critical illness was underestimated. Early physiological studies suggested that the right ventricle was of limited importance, as right-sided heart bypass experiments in animals showed minimal haemodynamic impact [24, 25]. However, subsequent research has highlighted the crucial role of the right ventricle in multiple pathological states, including left-sided heart failure, pulmonary hypertension (PH) and sepsis [26–28]. In ARDS, RV dysfunction is increasingly recognised as a major contributor to morbidity and mortality, yet it remains underdiagnosed and undertreated in intensive care settings.

This review focuses on the role of RV function in ARDS, providing an updated overview of its pathophysiological implications, diagnostic strategies and potential therapeutic interventions.

ARDS: definition and current treatment strategies

The global ARDS definition refines the 2012 Berlin criteria to enable faster diagnosis while reducing reliance on resource-intensive tests [1, 29]. ARDS is characterised as an acute condition occurring within 1 week of a known clinical insult or new/worsening respiratory symptoms [1, 29]. Diagnosis requires bilateral pulmonary infiltrates detectable *via* chest X-ray, computed tomography scan or lung ultrasound. Oxygenation impairment remains central, with oxygen saturation/fraction of inspired oxygen ratios applicable when oxygen saturation is $\leqslant$97% and arterial blood gas analysis is unavailable [1, 29]. Notably, the updated classification now includes nonintubated patients receiving high-flow nasal oxygen ($\geqslant$30 L·min^{-1}), noninvasive ventilation or continuous positive airway pressure, provided they meet other ARDS criteria [1, 29].

Over the past decades, multiple landmark studies have shaped ARDS management, emphasising lung-protective ventilation, prone positioning, fluid management, oxygen therapy and, in selected cases, neuromuscular blockade. These approaches have ultimately improving patient outcomes [3–11].

Lung-protective ventilation remains the cornerstone of ARDS treatment [7]. The ARDSNet trial demonstrated that low tidal volume ventilation (6 mL·kg^{-1} predicted body weight) significantly reduces mortality compared with traditional tidal volumes (12 mL·kg^{-1}), making it standard care [7]. Beyond tidal volume reduction, research has highlighted driving pressure as a key determinant of survival [30]. A large observational study found that lower driving pressures correlate with improved survival, underscoring the importance of optimising ventilatory settings [30].

Prone positioning provides significant mortality benefits, particularly in severe ARDS. The Proning Severe ARDS Patients (PROSEVA) trial demonstrated that early and prolonged prone positioning ($\geqslant$16 h·day^{-1}) nearly halved mortality compared with supine positioning [6]. This effect is attributed to improved ventilation/perfusion (V'/Q') matching, better lung mechanics and reduced lung stress, establishing prone positioning as a key intervention in moderate to severe ARDS.

iNO has been investigated for its selective pulmonary vasodilatory effects. While studies show iNO transiently improves oxygenation, reduces PAP and increases cardiac output, it does not confer a survival benefit [31–34]. Subsequent trials confirmed these findings and raised concerns about renal impairment, limiting the routine use of iNO to select cases requiring temporary oxygenation support [35, 36].

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Oxygen therapy must also be carefully managed to avoid hyperoxia-induced lung injury as well as excessive hypoxia. The Liberal Oxygenation *versus* Conservative Oxygenation in ARDS ($LOCO_2$) trial compared partial pressure of oxygen (P_{aO_2}) targets of 90–105 mmHg and 55–70 mmHg and found that the lower target may increase mortality [37]. A network meta-analysis based on 10 randomised controlled trials found increased mortality associated with a P_{aO_2} target of >150 mmHg compared with lower targets in critically ill patients requiring respiratory support [38]. These results emphasise the need for appropriately targeted oxygen delivery.

Fluid management strategies have also evolved to optimise oxygenation and prevent pulmonary oedema. The Fluids and Catheters Treatment Trial (FACTT) demonstrated that a conservative fluid strategy improves oxygenation, shortens mechanical ventilation duration and reduces the length of time spent in the intensive care unit (ICU) without increasing organ failure risk, compared with a liberal fluid strategy [39].

Neuromuscular blockade has been explored as a means to reduce ventilator-induced lung injury. The ARDS et Curarisation Systematique (ACURASYS) trial suggested early administration of cisatracurium in moderate to severe ARDS improved oxygenation and potentially reduced mortality at 90 days [8]. However, the Re-evaluation of Systemic Early Neuromuscular Blockade (ROSE) trial later found no significant survival advantage, leading to neuromuscular blockade being reserved for cases with severe ventilator dyssynchrony or requiring deep sedation [40].

Taken together, these studies have established an evidence-based framework for ARDS management (figure 1), leading to improved survival and clinical outcomes. However, despite these advancements, mortality rates remain high, highlighting the need for continued research into novel therapeutic strategies. In this context, right-sided heart dysfunction (RHD) emerges as a critical yet often under-recognised factor.

RHD in ARDS: definition, pathophysiology and clinical relevance

RHD lacks a commonly accepted definition, though right-sided heart failure is generally understood as the inability of the right ventricle to sustain adequate cardiac output at normal filling pressures [41, 42]. Thus, the definition of RHD in ARDS is based primarily on echocardiographic and haemodynamic criteria, with

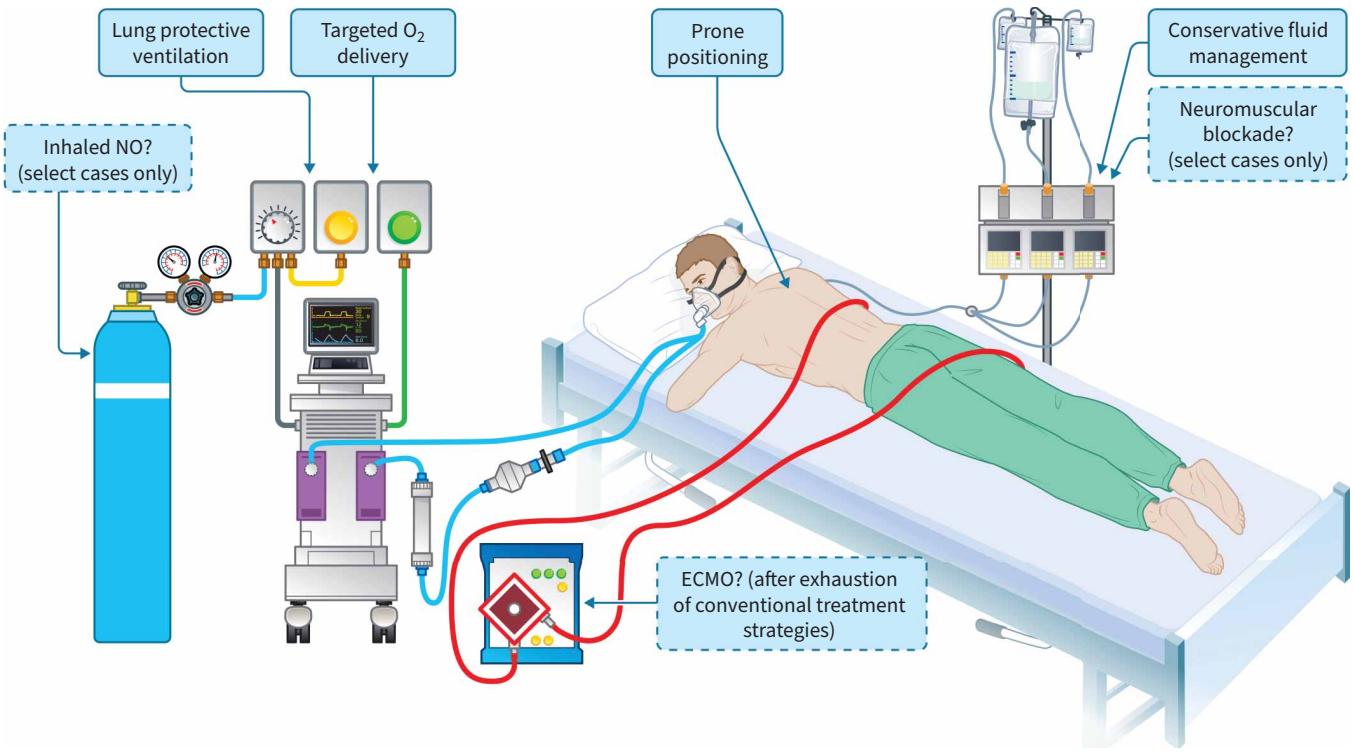
Lung protective ventilation
Targeted O_2 delivery
Prone positioning
Conservative fluid management
Neuromuscular blockade? (select cases only)
Inhaled NO? (select cases only)
ECMO? (after exhaustion of conventional treatment strategies)

FIGURE 1 Current strategies for the treatment of acute respiratory distress syndrome. ECMO: extracorporeal membrane oxygenation; NO: nitric oxide.

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a focus on acute cor pulmonale (ACP). The classic definition of ACP in ARDS includes RV dilatation, typically defined as an RV end-diastolic area to left ventricular end-diastolic area ratio greater than 0.6, combined with septal dyskinesia on echocardiography, in the absence of left ventricular failure or significant pre-existing PH [43–45]. Several studies have adopted this definition as clinically relevant. Other broader definitions of RHD incorporate additional findings such as RV dilatation, reduced RV fractional area change, impaired tricuspid annular plane systolic excursion (TAPSE) or evidence of elevated central venous pressure accompanied by clinical signs of systemic venous congestion [12, 46, 47]. In patients with ARDS without pre-existing chronic RHD (such as PH), RHD typically manifests as ACP, characterised by acute RV dilation and/or dysfunction [13]. The primary function of the right side of the heart is to pump mixed venous blood through the pulmonary circulation, facilitating forward venous return. However, because the pulmonary circulation operates as a low-pressure system, it is highly susceptible to afterload changes, making the right ventricle particularly vulnerable in ARDS [23].

Several pathophysiological mechanisms contribute to increased pulmonary vascular tone and subsequent RV afterload in ARDS, including hypoxic vasoconstriction (Euler–Liljestrand mechanism), hypercapnia, acidosis, *in situ* thrombosis and an imbalance between pulmonary vasoconstrictors and vasodilators (figure 2) [12, 19, 48]. Hypoxic vasoconstriction, while initially adaptive by redistributing blood flow away from poorly ventilated alveoli to maintain V'/Q' matching, can become maladaptive when

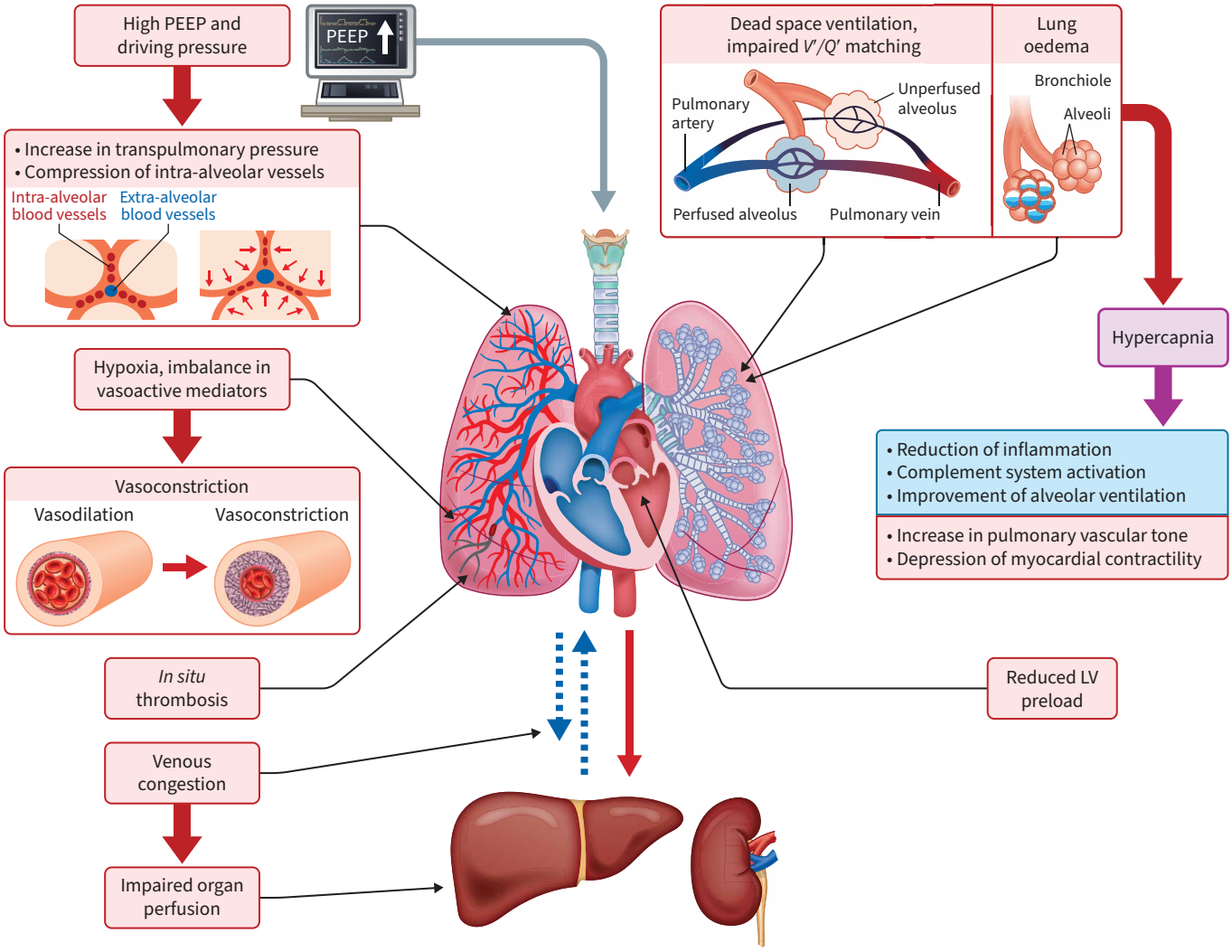

FIGURE 2 Right-sided heart dysfunction in acute respiratory distress syndrome. Vasoconstriction, compression of intra-alveolar vessels and *in situ* thrombosis contribute to increased right ventricular (RV) afterload. RV dysfunction leads to decreased left ventricular (LV) preload and venous congestion resulting in impaired organ perfusion. PEEP: positive end-expiratory pressure; V'/Q': ventilation/perfusion ratio.

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widespread, worsening RHD. Hypercapnia, often resulting from lung oedema, dead space ventilation and impaired V'/Q' matching, has both protective and harmful effects. While permissive hypercapnia can reduce inflammation, activate the complement system (C3 and C5) and improve alveolar ventilation, promoting better V'/Q' matching, it can also increase pulmonary vascular tone *via* calcium influx and depress myocardial contractility, aggravating RV-PA uncoupling [12, 49, 50]. This dual effect explains the observed correlation between elevated partial pressure of carbon dioxide and (right-sided) heart failure in several studies [13, 51, 52]. Notably, buffering respiratory acidosis in hypercapnic animal models worsened lung injury, supporting the rationale for permissive hypercapnia in ARDS [53, 54]. Clinically, a large retrospective study of patients with acute lung injury found no association between isolated hypercapnia and increased mortality, but prolonged hypercapnic acidaemia was linked to poor outcomes [55]. Despite these aspects, prospective studies evaluating the short- and long-term effects of hypercapnia, acidosis and buffering strategies in ARDS are still lacking.

Mechanical ventilation, a cornerstone in ARDS management, can worsen haemodynamic instability due to pathophysiological factors such as impaired lung compliance. To ensure adequate ventilation, both PEEP and driving pressure may need to be elevated, inadvertently increasing the transpulmonary pressure. This intensifies lung stress and strain. When transpulmonary pressures exceed pulmonary venous pressure, venous return is impaired and RV afterload rises [56, 57]. In ARDS, with its heterogeneous lung aeration, collapsed and aerated lung regions coexist, complicating the relationship between PVR and lung volume. High PEEP can exacerbate this by over-distending aerated alveoli, compressing intra-alveolar vessels and further increasing PVR, which places additional strain on the right ventricle. Consistent with this, clinical studies have linked high plateau pressures to increased RHD and mortality in ARDS, with high PEEP levels significantly reducing the RV stroke index [51, 58]. While driving pressure is strongly associated with RHD and survival, prospective evidence regarding the protective effects of low-pressure ventilation strategies on the right ventricle remains scarce.

Beyond increased RV afterload, RHD can have systemic implications, particularly renal dysfunction due to impaired organ perfusion and venous congestion [23]. In ARDS, volume overload can lead to RV dilation and the emergence or worsening of tricuspid regurgitation (TR), which may further reduce effective forward stroke volume and impair oxygen delivery [23]. Mechanical ventilation and elevated PEEP can exacerbate TR, adding to RV strain [59]. Although often under-recognised, TR in this context may contribute to circulatory failure and warrants careful fluid management [60]. Volume overload further exacerbates RV strain, setting off a vicious cycle of deteriorating RV function, interventricular septal bowing, reduced left ventricular preload (due to ventricular interdependence) and ultimately circulatory failure [23].

Of note, RHD in the setting of ARDS is highly relevant in the clinical setting, as patients with documented RHD have a higher need for prone positioning, vasoactive therapy and iNO [61]. Furthermore, a secondary analysis of FACTT data identified pulmonary vascular dysfunction as an independent predictor of mortality [62] and a meta-analysis of nine studies (1861 patients) showed a significant association between RV injury (dysfunction, failure or ACP) and mortality in patients with ARDS [63].

The majority of ARDS studies focus on RV systolic dysfunction, RV dilation and ACP, as these parameters are more directly associated with adverse outcomes in ARDS. In contrast, investigations into the relevance of RV diastolic dysfunction remain limited. Assessing RV diastolic function is challenging due to the complexity of parameters such as the end-diastolic pressure–volume relationship and derived indices including end-diastolic elastance, end-diastolic pressure, Tau, relaxation time and minimum value of the derivative of pressure with respect to time, which is an indicator of RV lusitropy. These measurements are not routinely performed in clinical practice, largely because reliable echocardiographic surrogates for RV diastolic function remain lacking [64]. However, evidence from the PH field highlights the importance of RV diastolic function for venous congestion, exercise capacity and survival, suggesting a potentially significant role of RV diastolic dysfunction in ARDS patients as well.

Given the complex interactions between pulmonary vascular changes, hypercapnia and systemic consequences, a deeper understanding of RHD in ARDS is essential for optimising treatment approaches and potentially improving patient outcomes.

Epidemiology and diagnostic approaches for RHD in ARDS

As hitherto described, RHD is a significant complication in ARDS, with studies reporting that approximately 20–50% of patients with ARDS exhibit signs of RHD [13–15]. The incidence of RHD is

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notably increased in patients with ARDS who also have conditions that inherently increase PVR, such as sepsis and acute pulmonary embolism [65]. Hypoxia and mechanical ventilation settings, especially high PEEP, may exacerbate RV strain and dysfunction. Given the high prevalence and impact of RHD in this cohort, early diagnosis is essential for improving clinical outcomes.

The diagnosis and management of RHD in ARDS require a multimodal, integrated approach that combines invasive haemodynamic monitoring, imaging techniques and noninvasive assessments [12, 23]. Haemodynamic assessment remains the gold standard for evaluating RV afterload [41]. Right-heart catheterisation (RHC), using the Swan–Ganz catheter, is instrumental in obtaining direct measurements of right atrial pressure, RV pressure, PAP and pulmonary artery wedge pressure [26]. These measurements enable the evaluation of RV afterload, contractility and compliance, all critical factors in understanding the pathophysiology of RHD. PVR, calculated from these parameters, remains a key marker for assessing RV function in ARDS.

However, the role of RHC in routine ARDS diagnosis has been questioned by large, randomised trials, including the FACTT, the Pulmonary Artery Catheters in Management of Patients in Intensive Care (PAC-Man) study and the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterisation Effectiveness (ESCAPE), which found no mortality benefit from routine use of pulmonary artery catheters in patients with acute heart failure [66–68]. Consequently, the use of RHC in ARDS has declined, but it may be used in selected cases based on clinical indication [2]. In certain high-risk cases, such as patients with PH or RV failure secondary to ARDS, RHC remains an essential tool to optimise ventilation strategies, manage fluid balance and guide inotropic therapy. Additionally, advanced haemodynamic techniques, including pressure–volume loop analysis and detailed RV pressure curve analysis, provide more nuanced information on RV function, although they are not yet routine in clinical practice and are limited to clinical studies currently [69]. Multi-beat pressure–volume loop analysis using the gold-standard conductance catheter with preload reduction is the state-of-the-art method for assessing load-independent contractility of the right ventricle and its adaptation to increased afterload (*i.e.*, RV-PA coupling). Given the complexities and potential risks of preload reduction, the single-beat approach may serve as a validated and practical alternative for assessing RV-PA coupling [70]. In a patient with COVID-19 and ARDS-associated RHD, pressure–volume loop analysis showed that prone positioning increased RV end-diastolic pressure and led to dilatation of the right side of the heart, subsequently impairing right-sided heart function (figure 3) [69]. This highlights the impact of positioning on RHD. Further studies utilising pressure–volume loop assessment to evaluate the effects of prone positioning on RHD are ongoing. A schematic illustration focusing on cardiac changes in RHD is shown in figure 4.

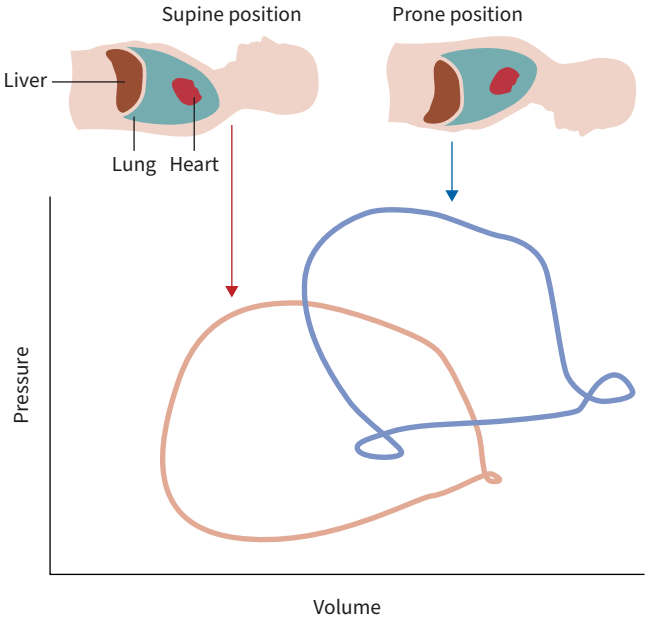

FIGURE 3 Effect of prone positioning on right ventricular function (pressure–volume loops) in acute respiratory distress syndrome.

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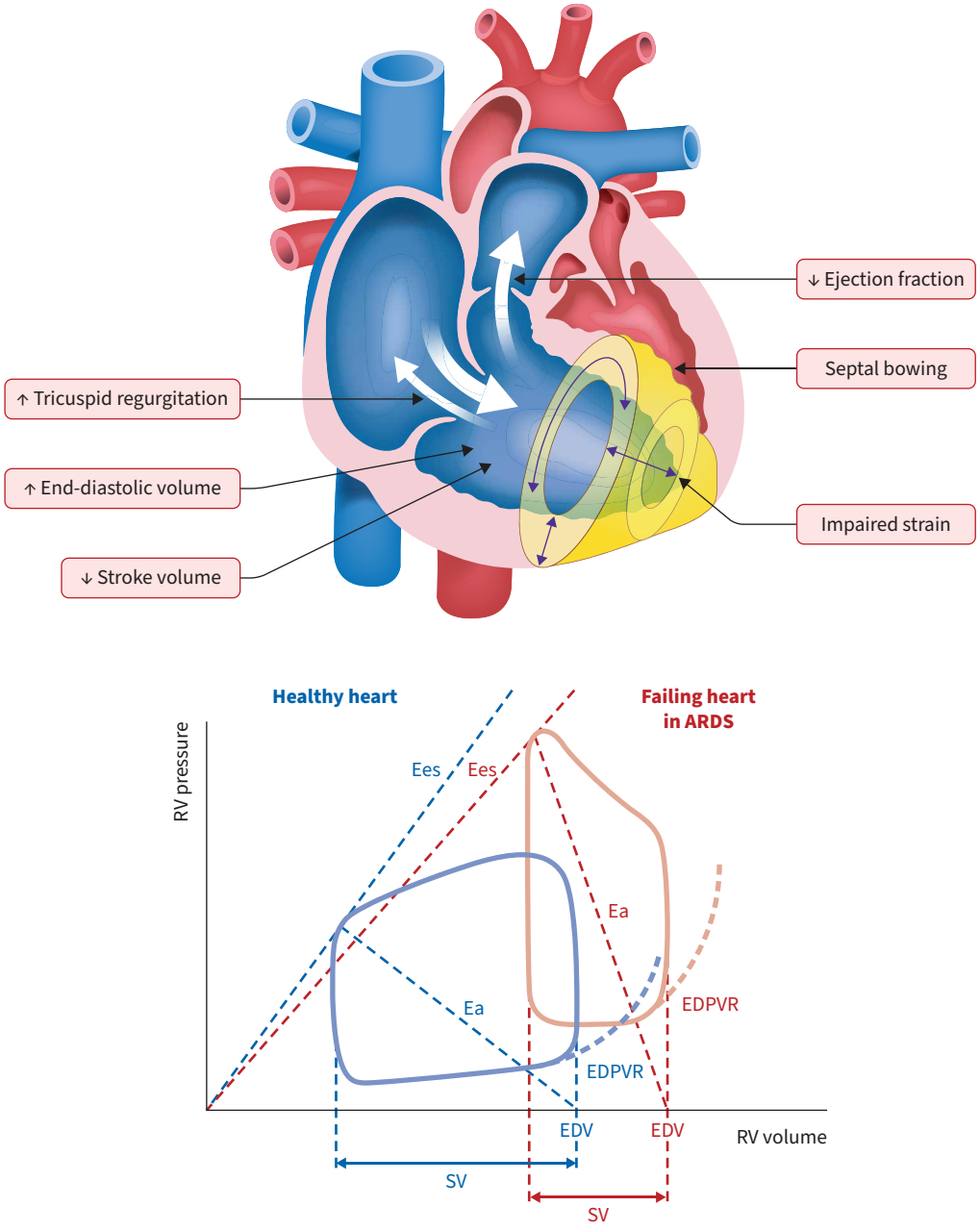

FIGURE 4 Cardiac changes in right heart failure. The schematic highlights key parameters affected in right heart failure. ARDS: acute respiratory distress syndrome; Ees: end-systolic elastance; Ea: arterial elastance. EDV: end-diastolic volume; SV: stroke volume; EDPVR: end-diastolic pressure–volume relationship; RV: right ventricular.

Noninvasive imaging, particularly transthoracic echocardiography, remains central to the diagnostic evaluation of RHD in ARDS [12]. Transthoracic echocardiography provides valuable, real-time information on RV size and function, including RV end-diastolic diameter, right atrial area and TAPSE, which serve as surrogates for RV systolic function. In patients with ARDS, the TAPSE/pulmonary artery systolic pressure (PASP) ratio is particularly useful for assessing RV-PA coupling and correlates well with invasive measures such as the elastance ratio, derived from pressure–volume loops [71]. Recent studies have highlighted the utility of three-dimensional echocardiography, which offers more precise volumetric assessments of RV function, allowing for better understanding of RV deformation patterns [72]. Advances in echocardiography-derived pressure–volume loops, which validate noninvasive RV function assessments against gold-standard conductance catheter-based methods, offer promising new diagnostic tools for

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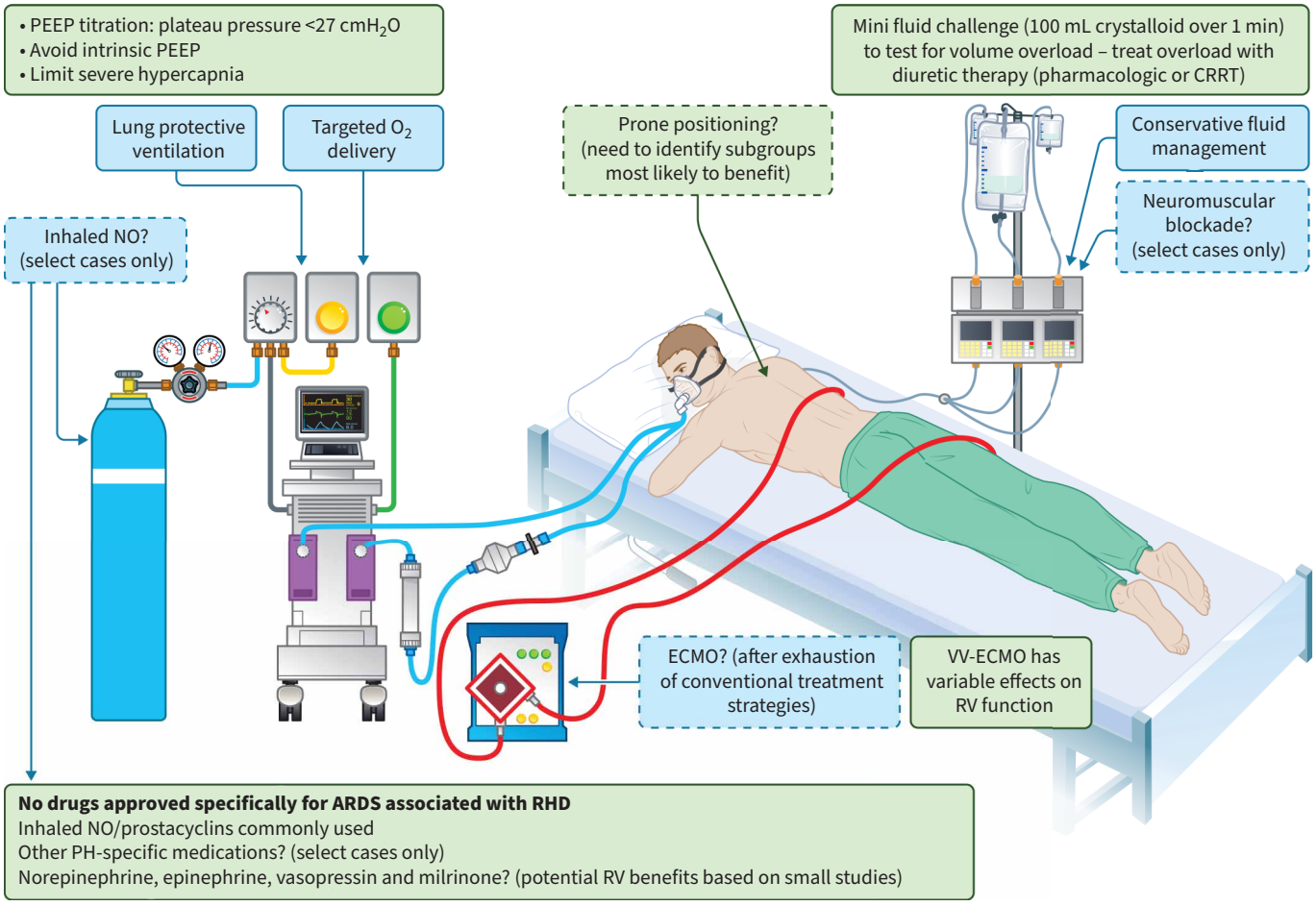
• PEEP titration: plateau pressure <27 cmH2O
• Avoid intrinsic PEEP
• Limit severe hypercapnia
Mini fluid challenge (100 mL crystalloid over 1 min) to test for volume overload – treat overload with diuretic therapy (pharmacologic or CRRT)
Lung protective ventilation
Targeted O2 delivery
Prone positioning? (need to identify subgroups most likely to benefit)
Conservative fluid management
Neuromuscular blockade? (select cases only)
Inhaled NO? (select cases only)
ECMO? (after exhaustion of conventional treatment strategies)
VV-ECMO has variable effects on RV function
No drugs approved specifically for ARDS associated with RHD
Inhaled NO/prostacyclins commonly used
Other PH-specific medications? (select cases only)
Norepinephrine, epinephrine, vasopressin and milrinone? (potential RV benefits based on small studies)

FIGURE 5 Strategies for the management of right-sided heart dysfunction (RHD) in acute respiratory distress syndrome (ARDS). Blue boxes show treatments for ARDS (as presented in figure 1); green boxes show adaptations/additional considerations for the treatment of RHD in ARDS. CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; NO: nitric oxide; PEEP: positive end-expiratory pressure; PH: pulmonary hypertension; RV: right ventricular; VV-ECMO: venovenous extracorporeal membrane oxygenation.

monitoring RV performance in ARDS, ultimately helping to understand the relevance of RHD in patients with ARDS [73]. The clinical role of cardiac magnetic resonance imaging and biomarkers (except for limited data on the usefulness of brain natriuretic peptide and/or troponin for risk assessment in patients with ARDS and RHD [74]) is currently limited.

Taken together, noninvasive imaging plays a crucial role in thoroughly assessing RV function. Relying solely on afterload parameters measured by RHC (*e.g.*, PAP) may be insufficient to fully evaluate RHD in ARDS patients.

Therapeutic strategies for managing RHD in ARDS

Management of ARDS, including mechanical ventilation and prone positioning, has a significant impact on right-sided heart function [12, 75, 76]. However, specific treatment options targeting RHD in ARDS remain limited. In essence, the treatment of RHD parallels that of other conditions affecting RV function, emphasising the optimisation of RV preload, contractility and afterload (figure 5). Specifically, PEEP is a key component of ARDS therapy, yet its effects on RV function are complex [77]. During mechanical ventilation, beyond optimising oxygenation and decarboxylation, it is crucial to consider strategies for protection of the right side of the heart. Higher PEEP levels can increase RV afterload, leading to decreased stroke volume, increased RV end-diastolic volume and reductions in TAPSE and cardiac index. As studies on the impact of PEEP on RV function and cardiac output yield inconsistent results, multicentre trials are needed to determine optimal PEEP strategies in patients with ARDS and RHD.

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PEEP titration plays a critical role in mitigating RV dysfunction. Compliance-guided and transpulmonary pressure-oriented PEEP selection appear superior to using the lower inflection point of the pressure–volume curve and PEEP titration based on ARDSNet recommendations, respectively, as they are associated with better RV performance [56, 78]. Recruitment manoeuvres transiently decrease cardiac index and elevate mean PAP, but these effects typically return to baseline afterwards [79, 80]. High-frequency oscillatory ventilation, though rarely used in adult ICUs, has been shown to increase mean PAP and PVR while reducing cardiac index [20]. Additionally, higher respiratory rates contribute to lower cardiac index due to increased dead space ventilation and intrinsic PEEP. Of note, lung volume plays a crucial role, as both low and high lung volumes affect RV afterload. PVR in intra- and extra-alveolar vessels is generally minimised when lung volume is close to functional residual capacity [81]. For RV protective ventilation, maintaining a plateau pressure below 27 cmH_2O is essential to prevent ACP [82]. Additionally, avoiding intrinsic PEEP and limiting severe hypercapnia can positively influence the geometry and function of the right side of the heart [82].

Prone positioning is an established intervention in moderate to severe ARDS and may improve RV function by reducing RV dilation and increasing cardiac index [83]. However, findings remain inconsistent, with some studies demonstrating improvements while others report decreases in stroke volume and RV ejection fraction [69]. The haemodynamic effects of prone positioning on RHD require further investigation, particularly using advanced imaging and invasive monitoring.

Both low filling and volume overload of the right ventricle can impair cardiac output by significantly altering heart geometry, leading to RV dilation and ventricular interdependence with compromised left ventricular filling. Fluid challenge is commonly used to assess fluid responsiveness in various conditions and may predict uncoupling of the right ventricle [84]. In ARDS, a mini fluid challenge of 100 mL crystalloid over 1 min appears to be a reasonable option for testing. If volume overload is present, diuretic therapy, whether pharmacologic or *via* continuous renal replacement therapy, may be necessary, but caution is required to avoid overdiuresis and subsequent RV underfilling [85].

Inhaled pulmonary vasodilators, such as iNO and prostacyclins, are commonly used to modulate pulmonary vascular tone in patients with ARDS and RHD [86, 87]. Administration of iNO reduces mean PAP and PVR and may improve RV ejection fraction and cardiac output [87, 88]. Some data suggest a potential mortality benefit, but the haemodynamic improvements are often transient, with deterioration upon discontinuation. PH-specific medications, including sildenafil and epoprostenol, may also lower PVR and enhance cardiac output, but are rarely used for ARDS-related RHD [86, 89]. Combination therapy, such as noradrenaline with iNO, may provide superior haemodynamic effects compared with iNO alone [90]. Levosimendan, a calcium sensitiser and inodilator, has been reported to improve RV systolic function and enhance cardiac index through reductions in mean PAP and PVR [91]. However, despite these promising therapies, no pharmacologic treatment is specifically approved for ARDS-associated RHD. In select cases, PH drugs, particularly phosphodiesterase-5 inhibitors including sildenafil and tadalafil and prostacyclin derivatives such as epoprostenol and treprostinil, may be used to reduce RV afterload [76]. Commonly used vasoactive drugs may also be beneficial for treating RHD in ARDS, including norepinephrine, epinephrine, vasopressin, dopamine, dobutamine and milrinone [76]. However, these agents come with potential side-effects, such as arrhythmias, reduced systemic vascular resistance or even increased PVR (*e.g.*, phenylephrine) [76]. Small-scale studies suggest that norepinephrine, epinephrine, vasopressin and milrinone, in particular, may improve RV-PA coupling [76].

Extracorporeal life support, including VV-ECMO, is often necessary in severe ARDS, but its impact on RV function remains complex [92]. While the Conventional Ventilatory Support *versus* Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial suggested a potential association between extracorporeal membrane oxygenation (ECMO) as an adjunct to optimal conventional ARDS management and improved survival, concerns about methodological limitations persist [93]. The ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial found no significant difference between early ECMO (with ultra-protective ventilation) and conventional treatment with rescue ECMO [5]. Consequently, current guidelines recommend exhausting conventional treatment strategies, including the prevention and management of ACP, before considering ECMO therapy [94, 95]. Notably, VV-ECMO has variable effects on RV function [92]. In particular, one study showed reductions in central venous pressure and mean PAP without a clinically relevant improvement in cardiac index [96], while a case report suggested early stabilisation of the interventricular septum following ECMO implantation [97]. One advantage of VV-ECMO is the ability to implement ultra-protective ventilation strategies; this combination may lower PASP although it does not necessarily improve RV function [98].

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The ProtekDuo (LivaNova PLC, London, UK) is a dual-lumen cannula designed for single-site access *via* the right internal jugular vein, allowing percutaneous insertion and advancement through the right heart, with its tip positioned in the main pulmonary artery. This design facilitates temporary RV unloading *via* RV bypass and may improve haemodynamics in ARDS patients with RV dysfunction. However, due to its transvalvular positioning, the ProtekDuo may induce TR or rhythm disturbances, as also seen with other intracardiac devices [99]. Nonetheless, outcomes appear comparable to those of conventional RV assist device cannulation strategies, as reported by Saeed *et al*. [100]. Thus, the ProtekDuo cannulation strategy might be a feasible alternative or addition in selected patients in need of VV-ECMO.

While VV-ECMO is standard in severe ARDS, veno-arterial ECMO may be considered in select cases with severe (right) heart dysfunction or refractory shock. Given its higher complication rate and lower survival compared to VV-ECMO, its use should be limited to carefully selected ARDS patients [101–104].

Additional circulatory support strategies, such as the intra-aortic balloon pump in combination with VV-ECMO, have been associated with further reductions in central venous pressure and improvement of RV function [92, 105]. However, their impact on RHD remains inadequately studied. Extracorporeal carbon dioxide removal appears to augment cardiac output and, when combined with ultra-protective ventilation (tidal volume of 4 $mL \cdot kg^{-1}$ ideal body weight), has been linked to improved RV function, as indicated by enhanced TAPSE [92]. Nonetheless, the evidence remains limited owing to small study populations, necessitating further trials.

Future directions in ARDS and right-sided heart management

Advancing the management of ARDS-related RHD requires a better understanding of diastolic function, which is possible through novel echocardiographic parameters and conductance catheterisation [64]. Determining optimal PEEP settings based on pressure–volume loop analysis may enable a more individualised approach, minimising RV overload while optimising lung mechanics. Furthermore, the impact of prone positioning on RV function should be investigated using advanced imaging modalities and continuous haemodynamic monitoring to delineate patient subgroups most likely to benefit from this intervention. Despite significant advancements in mechanical support and pharmacologic therapies, the management of RV dysfunction in ARDS remains challenging due to patient heterogeneity. Large-scale clinical trials are necessary to improve therapeutic algorithms and identify the most effective strategies for specific patient populations.

Additionally, recent evidence highlights a strong link between RHD and multi-organ impairment in PH, which is a complication of ARDS, particularly in the setting of acute RV failure, which may be extrapolated to ARDS populations with concomitant RV involvement. In PH, RV dysfunction leads to systemic venous congestion, impaired forward flow and organ hypoperfusion, which are mechanisms that contribute significantly to hepatic and renal dysfunction [106, 107]. Congestive hepatopathy and ischaemic hepatitis are well-recognised consequences of elevated right atrial pressure and venous congestion, with liver stiffness correlating closely with impaired RV and right atrial function, tricuspid insufficiency and adverse clinical outcomes. Both low cardiac output and venous congestion are key drivers of end-organ dysfunction in PH, affecting the kidney, liver and gut systems. These mechanisms are well described in PH and likely extend to critically ill patients with RV failure [107, 108].

Taken together, key questions for future studies are as follows:

1) Can pressure–volume loop analysis be used to personalise PEEP titration in ARDS, balancing lung protection with RV unloading?
2) Which patient subgroups benefit most from prone positioning in terms of RV function and haemodynamics?
3) How can we stratify ARDS patients by RV phenotype to tailor pharmacologic and mechanical interventions more effectively?
4) What are the long-term consequences of RV dysfunction in ARDS survivors and how can these be mitigated?
5) How does right ventricular dysfunction contribute to the development of multi-organ failure in patients with ARDS?
6) Which easy-to-assess RV functional and haemodynamic parameters are associated with outcome?
7) What is the association between RHD and multi-organ dysfunction in ARDS?

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Points for clinical practice

- RHD is a critical aspect of ARDS.
- The diagnosis and management of RHD in ARDS require an integrated approach that combines invasive haemodynamic monitoring, imaging techniques and noninvasive assessments.
- Titration of PEEP, including maintaining a plateau pressure below 27 cmH_2O, avoiding intrinsic PEEP and limiting severe hypercapnia, plays a critical role in mitigating RHD.
- If volume overload is present, diuretic therapy may be necessary, but caution is required to avoid overdiuresis and subsequent RV underfilling.
- Inhaled pulmonary vasodilators, such as nitric oxide and prostacyclins, are commonly used to modulate pulmonary vascular tone in patients with ARDS and RHD. However, no pharmacologic treatment is specifically approved for ARDS-associated RHD.
- The impact of ECMO on RV function is complex. Conventional treatment strategies, including the prevention and management of ACP, should be exhausted before considering ECMO therapy.

Questions for future research

- Advancing the management of ARDS-related RHD requires a better understanding of diastolic function, which is possible through novel echocardiographic parameters and conductance catheterisation.
- Multicentre trials are needed to determine optimal PEEP strategies in patients with ARDS and RHD.
- The impact of prone positioning on RV function should be investigated using advanced imaging modalities and continuous haemodynamic monitoring to delineate patient subgroups most likely to benefit from this intervention.
- Large-scale clinical trials are necessary to improve therapeutic algorithms and identify the most effective strategies for specific patient populations.

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